

*DOI:*
10.1016/j.jid.2017.12.016

*Document Version*
Peer reviewed version

# Accepted Manuscript


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PII: S0022-202X(17)33310-9

DOI: 10.1016/j.jid.2017.12.016

Reference: JID 1226

To appear in: *The Journal of Investigative Dermatology*

Received Date: 27 November 2017

Revised Date: 1 December 2017

Accepted Date: 1 December 2017

Please cite this article as: Uitto J, Bruckner-Tuderman L, McGrath JA, Riedl R, Robinson C, EB2017 - Progress in Epidermolysis Bullosa Research Towards Treatment and Cure, *The Journal of Investigative Dermatology* (2018), doi: 10.1016/j.jid.2017.12.016.

*Journal of Investigative Dermatology*
Meeting Report
12/12/2017
JID-2017-1010 FINAL

# EB2017 - Progress in Epidermolysis Bullosa Research Towards Treatment and Cure

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Running title: Progress in EB research and treatment

Abbreviations: EB, epidermolysis bullosa; EBS, EB simplex; JEB, junctional EB; DEB, dystrophic EB

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**ABSTRACT**

Epidermolysis bullosa (EB), a group of heritable blistering disorders, demonstrates extensive phenotypic variability due to mutations in as many as 20 distinct genes. There is no cure for this devastating group of disorders, however, a number of preclinical developments show promise, and some approaches have already reached the stage of early clinical trials. Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International, a global coalition of national patient organizations advocating on behalf of the patients and families with EB, supports research and organizes periodic scientific and clinical meetings on this disease. The latest one, EB2017, was held in the context of the European Society for Dermatological Research Meeting in Salzburg in September, 2017. This Report summarizes some of the recent research and clinical developments which have identified promising avenues towards treatment and perhaps eventual cure, with improved quality of life for patients with EB.

## INTRODUCTION

Epidermolysis bullosa (EB) is a highly heterogeneous group of skin fragility disorders with extensive phenotypic variability and diverse clinical outcomes (for review, see (Fine *et al.*, 2014). The diagnostic hallmark of this group of diseases is blistering of the skin as a result of minor trauma, leading to erosions and non-healing ulcers. In certain subtypes, these findings are associated with mutilating scarring and early development of aggressive squamous cell carcinomas. In spite of tremendous progress made over the last quarter of a century in understanding the molecular genetics and the pathomechanistic pathways in this group of disorders, there is no cure as yet.

DEBRA International, a coalition of national patient organizations, funds research and advocates on behalf of the patients and families with EB. Towards this goal, DEBRA International organizes periodic research and clinical meetings for investigators working on EB, and in related fields, to allow review of the state-of-the-art and to provide a platform for exchange of ideas for research prioritization (Bruckner-Tuderman *et al.*, 2013; Uitto *et al.*, 2010; Uitto *et al.*, 2016). To reflect the accelerating translation of research into clinical application, DEBRA International organized its latest research conference, EB2017, for the first time in conjunction with the annual EB-CLINET clinical conference, in Salzburg, Austria (September 24$^{th}$-27$^{th}$, 2017). This meeting was attended by over 250 scientists and clinicians (Figure 1). This synopsis summarizes some of the findings reported in this conference.

## IDENTIFICATION OF NOVEL GENES AND MUTANT ALLELES WITH CLINICAL IMPLICATIONS

The heritable forms of EB were initially divided into three broad categories based on the level of blistering within the skin as visualized by transmission electron microscopy, *viz.*, simplex (EBS), junctional (JEB) and dystrophic (DEB) subtypes (Fine *et al.*, 2014). While this early classification was somewhat helpful for prognostication, it was clear that each of these three categories represent a spectrum of severity and outcome. This phenotypic variability was subsequently shown to reflect mutations in 10 distinct genes expressed within the cutaneous basement membrane zone. Subsequently, Kindler syndrome (KS) was proposed to be the fourth subtype of EB, and demonstrations of mutations in *FERMT1* brought the number of mutated genes to 11 (Jobard *et al.*, 2003; Siegel *et al.*, 2003). More recently, a number of genes, primarily expressed within the epidermis and largely associated with EBS, brought the total number of mutant genes to 18 (Table 1). At the end of 2016, several investigators independently identified mutations in a novel gene, *KLHL24*, in a significant number of patients with EBS (He *et al.*, 2016; Lee *et al.*, 2017; Lin *et al.*, 2016). Finally, quite recently, a patient with a Kindler syndrome-like clinical presentation, including early blistering which subsided with age and nephropathy was found to harbor a homozygous splicing mutation in *CD151*, encoding a tetraspanin (TM4) that is expressed at the cutaneous basement membrane zone (Vahidnezhad *et al.*, 2017a). These observation, together with previously published cases with similar clinical presentations, suggested that the total number of genes harboring mutations in different subtypes of EB is at least 20 (Table 1).

Identification of mutations in candidate genes in different families with EB was originally based on PCR amplification of exons and flanking intronic sequences, followed by Sanger sequencing. Considering the large number of candidate genes in EB and the fact that many of these genes are large and multi-exonic, this approach has proven to be labor intensive, time

consuming and expensive. More recently, a number of next generation sequencing panels encompassing EB related genes have been developed, and this relatively inexpensive approach has markedly facilitated and streamlined mutation detection in families (Tenedini *et al.*, 2015; Vahidnezhad *et al.*, 2017c; Vahidnezhad *et al.*, 2017b). These panels have been supplemented with next generation sequencing approaches, including whole exome and whole genome sequencing, combined with homozygosity mapping in consanguineous families. These approaches have allowed rapid expansion of the mutation databases, and provided tools to identify family specific mutations for confirmation of the diagnosis with subcategorization and prognostication.

**REFINED PHENOTYPE/GENOTYPE CORRELATIONS**

Examination of mutation databases in the context of clinical presentations has allowed development of phenotype/genotype correlations, which now form the basis of prognostication, in general terms, based on mutations in newborns before phenotypic development is apparent. Advanced mutation detection strategies have also identified a number of unusual genetic constellations in patients with complex phenotypes, many of which were reported in the Symposium. For example, EBS with mottled pigmentation, which has previously been shown to result from a specific mutation (p.Pro25Leu) in *KRT5*, is now shown to also result from mutations in the *EXPH5* gene (Turcan *et al.*, 2016a). Mutations in *BPAG1-e* can cause an unusual EBS of an intermediate generalized phenotype with a prurigo papules (Turcan *et al.*, 2017). Large intragenic *KRT5* deletions have also been shown to account for some unsolved cases of EBS (Has *et al.*, 2017). Mutations in the *ITGB4* gene, frequently associated with an autosomal recessive form of JEB, can also result in an autosomal dominant form of EB (Turcan

*et al.*, 2016b). Unusual genetic alterations in *COL7A1* have also been linked to unusual phenotypes, as for example, large deletions targeting the triple helical domain of type VII collagen that cause acral dominant dystrophic EB (Chmel *et al.*, 2017). Also, a patient initially diagnosed with Shabbir syndrome, was found not to have mutations in *LAMA3* but in *LAMB3* instead (Vahidnezhad *et al.*, 2017b).

## PRECLINICAL DEVELOPMENT OF TREATMENT STRATEGIES

A spectrum of preclinical approaches has been utlized to develop treatment strategies for EB. Therapy approaches aimed at correcting the primary genetic defect at DNA, mRNA or protein levels extend from induced pluripotent stem (iPS) cell or keratinocyte-based gene correction and protein therapies to antisense oligonucleotides and premature termination codon (PTC) read-through drugs. Another line of treatment strategies includes disease-modifying, symptom-relief therapies, which address inflammatory and fibrotic processes that modify specific EB phenotypes.

### Preclinical development of iPS cell-based technologies

At the Symposium, several investigators reported that iPS cells can be derived from EB fibroblasts or EB keratinocytes which, in turn, can be re-differentiated after gene correction into keratinocytes and fibroblasts. A great advantage of iPS cell-based treatment approaches lies in the autologous nature of the cells that are generated and in the lack of immune reactions to corresponding tissue grafts. Significant technical advances in production, gene correction/gene editing and safety of GMP-quality iPS cells have been reported (Bilousova and Roop, 2014; Sebastiano *et al.*, 2014), and examples of quality criteria include minimal cellular heterogeneity

and high level of production of the corrected protein, *e.g.*, keratins 5 and 14 in cases of EBS and collagen VII in DEB. Furthermore, in order to improve graft quality, refinement of 3D organotypic cultures with iPS cell-derived keratinocytes and fibroblasts is being pursued (Shinkuma *et al.*, 2016). Finally, inducible pluripotent stem cells (iPSCs) have been established from revertant keratinocytes (Tolar *et al.*, 2014; Umegaki-Arao *et al.*, 2014), although clinical translation involving these cells has yet to be accomplished.

**Protein and mRNA-based approaches**

Prospects of protein therapy using recombinant human collagen VII have been investigated in the past few years. Initial observations in a preclinical mouse model suggested that intravenously administered collagen VII could reverse the disease phenotype in RDEB (Hou *et al.*, 2015), leading to the hypothesis that - in analogy to enzyme deficiencies that can be treated by infusions of recombinant enzymes - injections of GMP quality collagen VII might provide a useful therapeutic option for individuals with DEB. However, the development of the therapy turned out to be more challenging than anticipated, and this project has been taken over by industry partners (most recently, http://phoenixtissuerepair.com). It remains to be seen whether this line of treatment option can be successfully adapted from mouse models to humans. As an alternative, a planned early-stage trial of intradermal injection of recombinant human collagen VII, produced following optimization of post translational modifying enzymes (prolyl-4-hydroxylase, C-proteinase) to maximize stability and solubility, may offer a future option for localized therapy (P. Marinkovich, personal communication).

Therapeutic approaches targeting gene transcription have been tested mainly with *COL7A1* as a model. *In vitro* antisense oligonucleotide treatment of cells with mutant *COL7A1*

genes can lead to skipping of specific exons at RNA level, that when in frame, restores synthesis of essentially normal, although slightly shortened collagen VII (Bremer *et al.*, 2016; Turczynski *et al.*, 2016). Preclinical *in vivo* testing has shown that antisense oligonucleotide-based exon skipping can promote skin stability by partially functional collagen VII in DEB mice (Bornert *et al.*, 2016).

Another approach targeting gene transcription is based on read-through of premature termination codons (PTCs). The premise of this approach is that about 10% of genetic diseases are caused by nonsense mutations which introduce PTC and nonsense-mediated mRNA decay (Mort *et al.*, 2008). Aminoglycoside antibiotics, such as gentamicins, can induce PTC read-through. Gentamicins were first tested for their efficacy to induce PTC readthrough for *COL7A1 in vitro*, but their effects depend on the local nucleotide microenvironment of the mutations, and not all nonsense mutations are amenable to this kind of correction (Cogan *et al.*, 2014; Baradaran-Heravi *et al.*, 2017). In addition, the renal and oto- toxicities of aminoglycosides may prevent widespread clinical implementation. Nevertheless, a pilot trial assessed topical administration of gentamicin to the skin of five patients with RDEB and demonstrated enhanced collagen VII synthesis, suggesting that topical application may offer a therapeutic option with reduced systemic toxicity of gentamicin (Woodley *et al.*, 2017). Gentamicin preparations are mixtures of related molecules, and a minor gentamicin component, gentamicin B1, seems promising because of its potency as an inducer of the PTC read-through and its low toxicity (Baradaran-Heravi *et al.*, 2017). Another interesting compound is Amlexanox that induces PTC read-through and is thought to inhibit non-sense mediated mRNA decay. Amlexanox has been shown to increase mRNA expression and synthesis of full-length collagen VII in RDEB fibroblasts and keratinocytes with nonsense mutations (Atanasova *et al.*, 2017). This drug is

approved by FDA for other clinical indications, and its toxicity profile and pharmacokinetics have been established, thus facilitating its translation to clinical trials.

**Preclinical development of symptom-relief therapies**

Symptom-relief therapies are the current focus of EB research with the aim of counteracting subjective clinical findings, such as pain and itch as well as skin fibrosis, which greatly impair the quality of life of EB patients. Molecular mechanisms responsible for secondary processes are now being defined. In EBS, in addition to providing keratinocytes with structural stability against mechanical stress, keratin intermediate filaments regulate immune responses by controlling expression of IL-1, IL-18 and other cytokines. For example, the cytokine thymic stromal lymphopoietin (TSLP) is highly upregulated in EBS and mediates itch in keratin-deficient mice and patients (Kumar *et al.*, 2016). Keratins and other cytoskeleton-associated proteins also contribute to epidermal cell-cell adhesion via spatially and temporarily controlled stabilization of desmogleins and their suprastructures, desmosomes (Vielmuth *et al.*, 2017). Several other molecules have recently been identified that are altered upon breach of epidermal integrity and induce pro-inflammatory signaling (T. Magin, personal communication). Such molecules may become therapeutic targets in EBS, and perhaps in other forms of EB.

One of the most debilitating features of RDEB is progressive soft tissue fibrosis that causes joint contractures, deformities of the extremities and strictures at mucosal surfaces, particularly in the esophagus. The molecular and cellular mechanisms leading to these complications include inflammation and excessive TGF-ß signaling (canonical and non-canonical). Limiting these processes could substantially improve functionality and quality of life of the affected individuals. Losartan, an FDA-/EMA-approved drug, is known to inhibit

excessive TGF-ß signaling in some, but not all, fibrotic diseases. In RDEB mice, it efficiently reduced inflammation, TGF-ß activity, extracellular matrix accumulation, and progression of fibrosis (Nyström *et al.*, 2015). Recent investigations demonstrated that a parallel pathway involving signaling through the anti-fibrotic AT-2 and MAS receptors (Passos-Silva *et al.*, 2015) can be a target in RDEB. Toward this end, a phase-2 investigator-initiated clinical trial (Reflect study, EudraCT-No.: 2015-003670-32) explores safety and tolerability of losartan in children with moderate-to-severe RDEB and collects information on its efficacy (D. Kiritsi, personal communication).

Another approach to diminish systemic inflammation and fibrosis focuses on high-mobility group box 1 (HMGB1)-derived peptide as a potential drug. The HMGB1 factor is released from necrotic epithelial cells in RDEB and signals to bone marrow-derived mesenchymal stem cells, leading to their migration to circulation and homing to damaged skin (Aikawa *et al.*, 2015). In RDEB mice, the HMGB1-derived peptide prevented both skin fibrosis and gastrointestinal tract strictures and, importantly, extended the life-span of the mice significantly (K. Tamai, personal communication).

Collectively, preclinical development of biologically valid treatments shows encouraging promise for future therapies. In particular, remodeling of the dermal matrix by fibroblasts in the absence of collagen VII in RDEB results in key changes in gene-expression profiles and there is increasing evidence that this drives the development of aggressive SCC (Martins *et al.*, 2016). Notably, stromal modulators of TGF-β activity that, in turn, drive metastasis, angiogenesis and activation of fibroblasts (Costanza *et al.*, 2017), are likely targets for drug development to combat SCC in EB.

## EARLY CLINICAL TRIALS IN EB

Based on the progress made in understanding the genetic basis and pathomechanistic details of EB leading to skin fragility and extensive exploration of treatment opportunities at the preclinical level, the pipeline for clinical trials in EB has opened. In fact, 61 clinical trials involving EB patients are currently registered in clinical.trials.gov (USA), and 16 of these were registered in 2016-2017, reflecting acceleration of clinical trial activity in this disease (H. Rischel, personal communication). Additional clinical trials and observational studies registered in the European Union may be found at Eudract CT register (https://eudract.ema.europa.eu/results-web/), and worldwide at the World Health Organization register (http://www.who.int/ictrp/en/). Thus, diverse approaches to develop treatments that improve quality of life and provide eventual cures for EB patients are being pursued.

### Bone marrow transplantation

In 2010, the results of an early clinical trial of whole bone marrow transplantation (BMT) in six children with recessive DEB (RDEB) were reported (Wagner *et al.*, 2010). That study described clinical improvements in all subjects and five of the six showed increased collagen VII deposition at the dermal-epidermal junction. No individual was cured after BMT, but several showed a marked reduction in blister formation and substantial improvement in quality of life. However, toxicity relating to myeloablative conditioning was a concern because of high morbidity and mortality. Seven years on, this EB Symposium provided an opportunity to reflect on the BMT experience and its value for clinical application in EB. Globally, but mainly due to the considerable experience from the University of Minnesota, more than 40 children with either RDEB or JEB have now undergone BMT. Although detailed results of the clinical experiences

of the subsequent clinical trials have yet to be published, a number of lessons are emerging. Notably, (1) beneficial and sustained clinical responses, but not cures, continue to be noted in some, but not all, children with RDEB undergoing BMT; (2) mortality rates with revised conditioning protocols have decreased and are now ~15%; (3) some RDEB children show positive clinical improvement even in the absence of an increase in collagen VII in their skin; (4) experience of BMT in JEB is limited but, with occasional exceptions, BMT does not appear to have therapeutic benefit in this type of EB (J. Tolar, personal communication; (Hammersen *et al.*, 2016).

For families with children who have RDEB, many personal dilemmas remain: BMT is an experimental therapy and is being performed as part of a number of clinical trials; it should not be considered to be an approved therapy. The mortality risk and the uncertainty of the degree and mechanism of clinical response need to be weighed against the present status of translational research in RDEB, which is that BMT is currently the only treatment approach that has demonstrated a systemic impact on what is a systemic disease. There is clearly a need for the data from the extended clinical trials to be published as soon as possible, with a view to developing recommendations and caveats for use of BMT for EB.

**Cell therapy**

Previously, randomized double-blind clinical trials of intradermal injections of allogeneic fibroblasts into RDEB skin showed varying results on the extent or rate of re-epithelization of chronic erosions (Venugopal *et al.*, 2013; Petrof *et al.*, 2013). Nevertheless, a universal adverse finding was the considerable pain that results from injecting cells into often scarred skin. This type of local cell therapy has, therefore, now focused on delivering *COL7A1* gene therapy in

autologous fibroblasts to both intact skin and RDEB wounds (clinical trials.gov identifiers NCT02493816 and NCT02810951). In contrast, allogeneic cell therapy has progressed to systemic testing. An early phase clinical trial of intravenously administered allogeneic mesenchymal stromal cells (MSCs) in 10 children with RDEB showed improvements in wound healing, as well as reduction in pain and itch, and a positive impact on quality of life (Petrof *et al.*, 2015). A similar study in 10 adults with RDEB is currently being evaluated for safety and early efficacy (clinical trials.gov identifier NCT02323789). Clinical benefits appear to be sustained for up to 9 months, with further improvements after additional cell infusions, raising the possibility of repeated infusions of this form of mesenchymal stromal cell therapy having potential clinical utility. The likely benefits relate to the anti-inflammatory effects of the cells as skin biopsies have not shown any increase in collagen VII or new anchoring fibrils in the treated patients' skin. Indeed, additional preclinical work has shown that this type of systemic delivery cannot deliver adequate cell numbers needed to restore collagen VII expression at the cutaneous basement membrane zone (Kuhl *et al.*, 2015).

**Gene therapy**

Since the initial report of successful gene therapy based on grafting of *ex-vivo* corrected keratinocytes to the patient's skin in an individual with JEB, published in 2006 (Mavilio *et al.*, 2006), there have been few public reports of progress using this treatment for EB. In December 2016, however, the results of a single center clinical trial of ex-vivo cultures of RDEB keratinocytes, transduced with a retroviral vector containing full-length *COL7A1* cDNA, and re-grafted back onto the patient's wounds as epidermal sheets, were reported (Siprashvili *et al.*, 2016). There was evidence of wound healing and collagen VII expression in most samples,

although the clinical response was variable and generally declined over the following 12 months. However, the procedure was deemed safe and the data have provided a basis for expansion of this approach to further trials in more people with RDEB. A similar approach has been taken to correct the defect in a JEB patient with chronic non-healing ulcers in which grafting of the gene-corrected keratinocytes demonstrated remarkable healing (Bauer *et al.*, 2017). One potential criticism of ex-vivo/keratinocyte gene therapy approaches has often been that they can only be applied to a limited areas of skin, and thus it would be unlikely to have much impact on overall health and quality of life. However, this notion has recently been dispelled in an extraordinary account of the use of *ex-vivo* holoclone stem cell-derived keratinocyte gene therapy to replace over 90% of the skin of a 7-year-old boy with generalized intermediate JEB caused by *LAMB3* mutations (Hirsch *et al.*, 2017). The cost and general applicability of the approach remain controversial, but there can be no denying the incredible transformation in the life of the boy who was treated.

**Novel Topical Treatments**

Topical therapies, with easy applicability and low toxicity, remain an attractive avenue of translational research in EB, even if the therapeutic mechanisms underpinning such treatments are not fully known. A number of products have been, or are being, tested in proof-of-concept or later phase early clinical trials. For example, a betulin-rich triterpene extract from birch bark (Oleogel-S10, Birken AG) has been assessed in an open, blindly evaluated, controlled, prospective phase-2 pilot trial in wounds in individuals with DEB (EudraCT number 2010-019945-24). In evaluating 12 wound pairs in 10 subjects, there was a trend towards accelerated wound healing with the intervention but statistical significance was not demonstrable

(Schwieger-Briel *et al.*, 2017). A larger study to assess the reproduciblity of these preliminary observations is ongoing (J. Kern, personal communication).

The importance of controlled clinical trials in developing topical treatments for EB is emphasized by recent studies attempting to develop 6% allantoin as a new drug enhancing wound healing in EB (SD101; Amicus). Allantoin, has been previously shown to enhance epidermal wound healing in model systems, and early observations in a limited number of EB patients suggested beneficial effects. A large clinical trial involving more than 160 patients with different forms of EB indeed demonstrated improvement in the treated patients, however, the vehicle treated controls did equally well, probably reflecting the meticulous daily care of the patients enrolled in the trial. Thus, the study failed to demonstrate definitive improvement attributable to allantoin, but ongoing subgroup analysis may identify forms of EB and certain age groups that might benefit for this application.

DEBRA has, as a patient organization, supported EB research for over 30 years, from studies into the underlying pathology of EB through to proof-of-principle therapeutic concept studies and early-stage clinical trials. More recently, DEBRA has initiated studies, such as Prospective Epidermolysis Bullosa Longitudinat Evaluaton Study (PEBLES), to document the natural history of RDEB towards identification and validation of clinically appropriate parameters against which therapies may be evaluated in clinical trials. In recognition of the essential role of the biopharma industry as partners in developing therapies, DEBRA International organized an 'Industry Partnering Panel' workshop at EB2017, to consider how DEBRA can assist in overcoming common barriers faced by companies engaging in EB clinical trials. A consortium approach, engaging with industry and other stakeholders, is now in

development to address these challenges, and to expedite creation and delivery of clinical treatments.

## CONFLICT OF INTEREST

JU is the Chair of the DEBRA of America Medical and Scientific Panel. LBT has received research support from Tarix Orphan Ltd., Cambridge, MA. RR and CR are the President of DEBRA Austria and the Head of Research of DEBRA International, respectively.

## ACKNOWLEDGMENTS

The original research of the authors has been supported by grants from the DEBRA International.

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**FIGURE LEGEND**

**Figure 1.** Some of the participants in the joint DEBRA International EB2017 Research Symposium and EB-CLINET Clinical Conference held in Salzburg, September 24-27, 2017 (Photo courtesy of Dr. Rudolf Hametner).

**Table 1. Classification, Phenotypic Spectrum, and Molecular Heterogeneity of Epidermolysis Bullosa**

| Type of EB | Mutated Genes | Chromosomal Location | Protein | Inheritance | No. of Reported Mutations[a)] | Associated Phenotypes and Other Comments |
|---|---|---|---|---|---|---|
| **EBS** | *DSP* | 6p24.3 | Desmoplakin | AR | 265[b)] | Epidermolysis bullosa, lethal acantholytic |
| | *PKP1* | 1q32.1 | Plakophilin1 | AR | 16 | Ectodermal dysplasia/skin fragility syndrome |
| | *JUP* | 17q21.2 | Plakoglobin | AR | 40[c)] | Skin fragility, palmoplantar keratoderma, and woolly hair, with or without cardiomyopathy |
| | *KRT5* | 12q13.13 | Keratin 5 | AD | 151[d)] | 75% of all EBS cases; 14 cases of AR EBS-K14 have been reported |
| | *KRT14* | 17q21.2 | Keratin 14 | AD, AR | 114[e)] | |
| | *PLEC1* | 8q24.3 | Plectin | AR (AD) | 92 | Form of EBS; EB with pyloric atresia, EB with muscular dystrophy; Rare AD EBS-Ogna |
| | *DST* | 6p12.1 | BPAG1 | AR | 6 | |
| | *EXPH5* | 17q25.1 | Exophilin 5 | AR | 8 | |
| | *TGM5* | 10q24.3-q25.1 | Transglutaminase 5 | AR | 26 | Acral peeling skin syndrome |
| | *KLHL24* | 3q27.1 | Kelch-like protein in 24 | AD | 5 | EBS, generalized, with scarring and hair loss |
| **JEB** | *LAMA3* | 18q11.2 | Laminin-332 | AR | 48 | 9% of all JEB cases |
| | *LAMB3* | 1q32.2 | | AR | 112 | 70 % of all JEB cases |
| | *LAMC2* | 1q25.3 | | AR | 39 | 9% of all JEB cases |
| | *COL17A1* | 10q24.3-q25.1 | Collagen XVII | AR | 99[f)] | 12% of all JEB cases |
| | *ITGA6* | 2q31.1 | α6β4 integrin | AR | 8 | A few reported cases |
| | *ITGB4* | 17q25.1 | | AR (AD) | 95 | AD mode of inheritance reported in one study |
| | *ITGA3* | 17q21.33 | Integrin α3 subunit | AR | 11 | Four cases of EB reported with congenital nephrotic syndrome and interstitial lung disease |
| **DEB** | *COL7A1* | 3p21.31 | Collagen VII | AR, AD | 773 | 100% of all DEB cases |
| **KS** | *FERMT1* | 20p12.3 | Kindlin-1 | AR | 78 | 100% of all KS cases |
| **KS-like** | *CD151* | 11p15.5 | Tetraspanin CD151 | AR | 2 | EB with nephropathy |

[a)]The numbers represent the total number of distinct disease-associated mutations according to The Human Gene Mutation Database (www.hgmd.cf.ac.uk) as of 11/22/2017. Mutations in *KLHL24* not yet available on this database, were gathered from the three existing reports of *KLHL24*-associated EB, as summarized by Has, 2017 (Has, 2017).

[b)]In addition to EBS, mutations in *DSP* are related to following diseases: Arrhythmogenic right ventricular dysplasia 8 (OMIM:607450); Cardiomyopathy, dilated, with woolly hair and keratoderma (OMIM:605676); Dilated cardiomyopathy with woolly hair, keratoderma, and tooth agenesis (OMIM: 615821); Epidermolysis bullosa, lethal acantholytic (OMIM:609638); Keratosis palmoplantaris striata II (OMIM:612908); Skin fragility-woolly hair syndrome (OMIM:607655).

[c)]JUP mutations can cause AR Naxos disease (OMIM:601214); AD mutations can lead to arrhythmogenic right ventricular dysplasia 12 (OMIM:611525).

[d)]*KRT5* mutations are related to EBS and Dowling-Degos disease.

[e)]Mutations in *KRT14* cause different types of EBS (including with mottled pigmentation), as well as dermatopathia pigmentosa reticularis and Naegeli-Franceschetti-Jadassohn syndrome.

[f)]Mutations in *COL17A1* cause DEB and inherited epithelial recurrent erosion dystrophy (ERED)-like disease with eye manifestations only.

AR, autosomal recessive; AD, autosomal dominant